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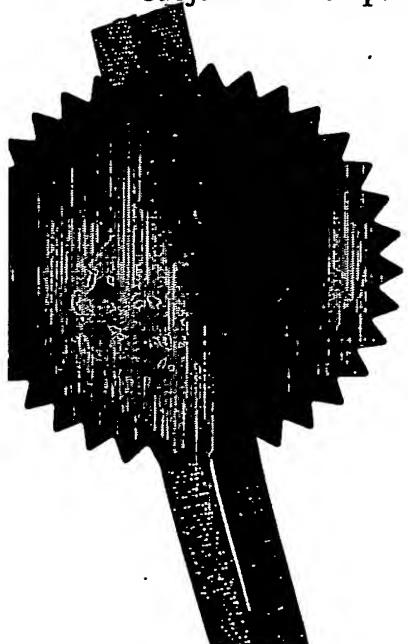
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Park, University Boulevard  
Nottingham NG7 2TN  
United Kingdom  
United Kingdom

Patents ADP number (*if you know it*)

7657521001

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention

INTRANASAL COMPOSITIONS

5. Name of your agent (*if you have one*)

ERIC POTTER CLARKSON  
PARK VIEW HOUSE  
58 THE ROPEWALK  
NOTTINGHAM  
NG1 5DD

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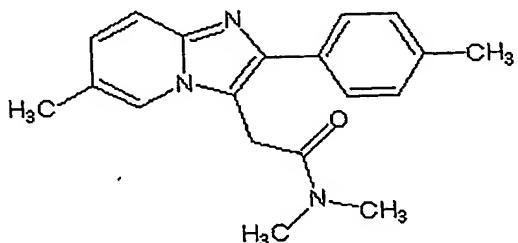
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## Intranasal compositions

This invention relates to pharmaceutical compositions for the intranasal administration of the compound zolpidem and its pharmaceutically acceptable salts.

Zolpidem (molecular weight 307.4) is N,N,6-trimethyl-2-(4-methylphenyl)-imidazo[1,2-a]pyridine-3-acetamide and has the following structure.



10

Zolpidem binds in the central nervous system to GABA<sub>a</sub> receptors containing the α<sub>1</sub> subunit and is a sedative/hypnotic used therapeutically for the short-term management of insomnia (see pages Z18-Z27, Therapeutic Drugs, Dollery (ed), 15 2<sup>nd</sup> edition, Churchill Livingstone, Edinburgh, 1999).

Zolpidem is typically administered therapeutically as the tartrate salt (MW 764.8). The adult dose is 10 mg (5 mg in elderly) by the oral route.

20 The present inventors have found that the intranasal route of administration can be advantageous for zolpidem and can offer significant benefits compared with administration via the oral route. In particular, it has been found that peak plasma concentrations can be reached much more rapidly when zolpidem is administered intranasally than when it is administered orally. Hence the nasal route can provide a more rapid onset of the therapeutic effects of zolpidem.

The present invention provides a composition for nasal delivery comprising zolpidem or a pharmaceutically acceptable salt thereof.

5 Zolpidem may be used as the free base or in the form of a pharmaceutically acceptable salt. Suitable pharmaceutically acceptable salts include, but are not limited to, the hydrochloride, mesilate, citrate, nitrate, lactate, maleate, tartrate, phosphate, succinate, fumarate and gluconate salts. Preferably zolpidem tartrate is used. It should be noted that zolpidem forms a "hemi" salt with  
10 tartaric acid in that the ratio of zolpidem to tartrate molecules is 2:1.

When producing a composition containing a salt of zolpidem, the appropriate salt may be used or zolpidem base may be dissolved *in situ* in a suitable acid.

15 The composition may be in any form suitable for nasal delivery. Suitable forms include aqueous or non-aqueous solutions and powders.

In one aspect, the present invention provides an aqueous solution comprising zolpidem or a pharmaceutically acceptable salt thereof, which is suitable for  
20 nasal delivery.

The aqueous solutions of the present invention preferably comprise zolpidem or a pharmaceutically acceptable salt thereof in a concentration of from 16 to 97 mg/ml (expressed as free base), more preferably from 20 to 90 mg/ml and  
25 most preferably from 24 to 80 mg/ml. Hence, when zolpidem is used in the form of the tartrate salt, the concentration of zolpidem tartrate is preferably from 20 to 120 mg/ml, more preferably from 25 to 110 mg/ml and most preferably from 30 to 100 mg/ml.

The viscosity of the aqueous solutions of the present invention is preferably less than 250 centipoise (cp), more preferably less than 200 cp and most preferably less than 150 cp.

5 The reported aqueous solubility of zolpidem tartrate is 23 mg/ml (*Merck Index*). It is therefore preferable that the solutions of the present invention include a solubility enhancing agent.

10 By the term "solubility enhancing agent" we mean a water-soluble ingredient (having a solubility in water of 10 mg/ml or greater) that, in the presence of zolpidem or a pharmaceutically acceptable salt thereof is able to increase the amount of zolpidem or salt that can dissolve. Thus, when zolpidem or a pharmaceutically acceptable salt is added to an aqueous solution containing the solubility enhancing agent, the amount of zolpidem or salt that will dissolve is higher than when zolpidem or salt is added to water only.

15 20 Suitable solubility enhancing agents include, but are not limited to poloxamers, polyethylene glycols, benzyl alcohol and cyclodextrins. Preferably, the solubility enhancing agent is a cyclodextrin.

25 Cyclodextrins are oligosaccharides made up of glucopyranose units and produced by the enzymatic degradation of starch. They are "bucketlike" or "conelike" toroid molecules with a rigid structure and a central cavity, the size of which varies according to the cyclodextrin type. The internal cavity of cyclodextrins is hydrophobic and may allow for the inclusion of lipophilic molecules, thus improving the aqueous solubility of poorly soluble drugs (Thompson, *Crit. Rev. Ther. Drug Carr. Sys.*, 14, 1-104, 1997).

20 The three major types of cyclodextrin (CD) are  $\alpha$ ,  $\beta$  and  $\gamma$  which comprise 6, 7 and 8 glucopyranose units respectively. To extend their usefulness as

pharmaceutical excipients, CDs, in particular  $\beta$ -CD, have been chemically modified, for example to produce derivatives that have enhanced aqueous solubility. Such derivatives include but are not limited to carboxymethyl- $\beta$ -CD, carboxymethyl-ethyl- $\beta$ -CD, diethyl- $\beta$ -CD, methyl- $\beta$ -CD, dimethyl- $\beta$ -CD, 5 trimethyl- $\beta$ -CD, randomly methylated  $\beta$ -CD, glucosyl- $\beta$ -CD, maltosyl- $\beta$ -CD, hydroxyethyl- $\beta$ -CD, 2-hydroxypropyl- $\beta$ -CD and sulfobutylether- $\beta$ -CD.

The preferred cyclodextrins for use in the present invention are  $\alpha$ -CD,  $\beta$ -CD;  $\gamma$ -CD and the modified derivatives of  $\beta$ -CD, such as 2-hydroxypropyl- $\beta$ -CD, 10 randomly methylated  $\beta$ -CD and sulfobutylether- $\beta$ -CD. Especially preferred cyclodextrins are  $\gamma$ -CD, 2-hydroxypropyl- $\beta$ -CD, randomly methylated  $\beta$ -CD and sulfobutylether- $\beta$ -CD (SBE-CD). Suppliers of  $\gamma$ -CD, hydroxypropyl- $\beta$ -CD and randomly methylated  $\beta$ -CD include ISP (Wayne, NJ, USA), Roquette (Lestrem, France) and Cerestar (Mechelen, Belgium). SBE-CD can be 15 obtained from CyDex Inc (Overland Park, KS, USA) under the trade name Captisol®.

The most preferred cyclodextrin for use in the solutions of the present invention is sulfobutylether- $\beta$ -CD (SBE-CD).

20 If the solutions of the invention comprise a cyclodextrin, the cyclodextrin is preferably present in an amount of from 50 to 700 mg/ml, more preferably from 75 to 500 mg/ml and most preferably from 100 to 400 mg/ml.

25 The present inventors have surprisingly found that cyclodextrins can enhance the rate of drug dissolution from the aqueous solutions into the nasal cavity.

The aqueous solutions of the invention preferably have a pH of from 3 to 8, more preferably from 3.5 to 7.5 and most preferably from 4.0 to 7.0. The pH

of the solutions may be adjusted to the desired value using any suitable organic or inorganic acid or organic or inorganic base. Suitable organic acids include, but are not limited to, acetic acid, citric acid, glutamic acid and methane sulfonic acid. Suitable inorganic acids include, but are not limited to, hydrochloric acid and sulphuric acid. Suitable organic bases include, but are not limited to, meglumine, lysine and tromethamine (TRIS). Suitable inorganic bases include, but are not limited to, sodium hydroxide and potassium hydroxide. Alternatively, or in addition, a buffer system may be included in the compositions in order to adjust and maintain pH. Examples of suitable buffer systems include, but are not limited to, a phosphate buffer comprising disodium hydrogen phosphate and potassium dihydrogen phosphate, and a citrate buffer comprising sodium citrate and citric acid.

The aqueous solutions of the invention may additionally comprise chitosan, a salt or derivative of chitosan or salt of a derivative of chitosan.

Chitosan is a cationic biopolymer comprising glucosamine and N-acetyl glucosamine that has bioadhesive properties and has been shown to improve the systemic bioavailability of certain drug compounds across mucosal surfaces such as the nasal cavity (see *Illum, Drug Discovery Today*, 7, 1184-1189, 2002).

By the term "chitosan" we include all derivatives of chitin, or poly-N-acetyl-D-glucosamine, including all polyglucosamines and oligomers of glucosamine materials of different molecular weights, in which the greater proportion of the N-acetyl groups have been removed through hydrolysis (deacetylation). In accordance with the present invention, the degree of deacetylation, which represents the proportion of N-acetyl groups which have been removed through

deacetylation, should preferably be in the range 40-97%, more preferably in the range 60-96% and most preferably be in the range 70-95%.

5 The chitosan, chitosan derivative or salt used in the present invention should preferably have a molecular weight in the range 10,000 to 1,000,000 Da, more preferably in the range 15,000 to 750,000 Da and most preferably in the range 20,000 to 500,000 Da.

10 Salts of chitosan are suitable for use in the present invention. Salts with various organic and inorganic acids are suitable. Such suitable salts include, but are not limited to the nitrate, phosphate, glutamate, lactate, citrate, hydrochloride and acetate salts. Preferred salts are the hydrochloric acid and glutamic acid salts.

15 Chitosan derivatives and their salts are also suitable for use in this invention. Suitable chitosan derivatives include, but are not limited to, esters, ethers or other derivatives formed by bonding acyl and/or alkyl groups with the hydroxyl groups, but not the amino groups of chitosan. Examples include O-alkyl ethers of chitosan and O-acyl esters of chitosan. Modified chitosans, such as those 20 conjugated to polyethylene glycol may be used in the present invention. Conjugates of chitosan and polyethylene glycol are described in WO99/01498.

25 Chitosans suitable for use in the present invention may be obtained from various sources, including Primex, Haugesund, Norway; NovaMatrix, Drammen, Norway; Seigagaku America Inc., MD, USA; Meron (India) Pvt, Ltd., India; Vanson Ltd, VA, USA; and AMS Biotechnology Ltd., UK. Suitable derivatives include those that are disclosed in Roberts, Chitin Chemistry, MacMillan Press Ltd., London (1992).

Particularly preferred chitosan compounds that may be mentioned include chitosan glutamate (available as Protasan UPG213 from NovaMatrix, Drammen, Norway).

5 The concentration of chitosan in the aqueous solutions is preferably from 0.5 to 50 mg/ml, more preferably from 0.75 to 35 mg/ml and most preferably from 1 to 20 mg/ml.

10 A preferred aqueous solution of the present invention comprises from 30 to 60 mg/ml of zolpidem tartrate, from 100 to 300 mg/ml SBE-CD and from 2 to 10 mg/ml of chitosan glutamate.

15 The aqueous solutions containing chitosan, a salt or derivative thereof or a salt of a chitosan derivative preferably have a pH of from 3 to 6, more preferably from 3.5 to 5.8 and most preferably from 4.0 to 5.6. The pH of the chitosan containing solutions may be adjusted as described earlier although it is preferred not to use citrate salts as the use of citrate salts can result in precipitate formation in the presence of chitosan.

20 Surprisingly, the present inventors have found that the use of chitosan, a salt or derivative thereof or a salt of a derivative of chitosan increases the extent of intranasal absorption of zolpidem in the form of a complex with SBE-CD. By "increased extent of absorption", we mean that the maximum plasma concentration ( $C_{max}$ ) and bioavailability are higher compared to a composition 25 that contains no chitosan and given at the same zolpidem dose.

The water used to prepare the solutions of the present invention can be boiled and cooled and/or purged with a gas such as helium in order to minimise the dissolved oxygen content and hence maximise drug stability. Purified water

such as water for injections may be used in the compositions of the present invention.

5 The compositions of the invention may, alternatively, be in the form of a non-aqueous solution or a powder composition.

10 Solvents that may be used to prepare the non-aqueous solutions of the invention include, but are not limited to ethanol, propylene glycol, polyethylene glycol, glycofurool, benzyl benzoate and polyoxyethylene castor oil derivatives, such as Cremophor® (BASF, Germany). The concentration of 15 zolpidem in the non-aqueous solutions of the invention is typically as described above for the aqueous solutions.

15 The solutions of the present invention may also contain other pharmaceutically acceptable ingredients well known in the art. Such ingredients include, but are not limited to, antioxidants (for example sodium metabisulphite), chelating agents (such as edetic acid or one of its salts), preservatives (such as potassium sorbate, parabens, phenylethyl alcohol or benzalkonium chloride), flavours, sweeteners, thickening, adhesive or gelling agents, including, but not limited 20 to, celluloses such as hydroxypropyl methylcellulose, methylcellulose, hydroxypropyl cellulose, sodium carboxyl cellulose and microcrystalline cellulose, poloxomers, polyethylene glycols, carbomers or polyethylene oxide.

25 Preferably the solutions of the invention contain a preservative and/or are sterile. If preservatives are omitted from the compositions, microorganisms may be removed using any suitable method known in the art, for example by making the compositions aseptically or by terminally sterilising them.

Preferably the compositions of the invention are non-pyrogenic.

Methods of formulating drug substances for administration in a powder form are well known to those skilled in the art. For example, the powder formulations of the present invention may be in the form of a blend of drug powder with other ingredients, as granules or as microspheres.

The powder compositions of the present invention may comprise a cyclodextrin. Suitable cyclodextrins are described above. The most preferred cyclodextrin for use in the powder compositions is SBE-CD. The present inventors have surprisingly found that cyclodextrins can enhance the rate of drug dissolution from the powder compositions into the nasal cavity.

When the powder compositions of the present invention comprise a cyclodextrin, the cyclodextrin may be incorporated into the powder blend, granules or microspheres in solid (powder) form. Alternatively, the zolpidem or salt thereof may be partially or completely pre-dissolved in an aqueous cyclodextrin solution and the water then removed to produce zolpidem-cyclodextrin inclusion complex in solid form. Suitable methods for removal of water from such a solution include spray drying, freeze-drying, vacuum drying and oven drying.

A powder blend according to the present invention may be prepared by mixing zolpidem or a pharmaceutically acceptable salt thereof with inert ingredients that are standard in the art. Such inert ingredients include, but are not limited to diluents such as calcium phosphate, lactose, sugars such as dextrose and sucrose, polyols such as mannitol and sorbitol, and microcrystalline cellulose, glidants such as colloidal silica and lubricants such as magnesium stearate and hydrogenated vegetable oil and surfactants such as polysorbates; and

polyethylene glycol. The powder blend may optionally contain chitosan, a salt or derivative or a salt of a derivative of chitosan.

For preparing a uniform powder blend on a small scale, a pestle and mortar 5 and/or sieve may be appropriate whereas mechanical mixers are required for larger scale manufacture. There are numerous types of mixer available and these are widely described in the literature, for example Chapter 37, Remington: The Science and Practice of Pharmacy, 20<sup>th</sup> Edition, Lipincott, Williams and Wilkins, Baltimore, 2000.

10

Alternative processes for preparing the formulations of the invention include spray drying, granulation and supercritical fluid processes.

If the powder composition of the invention comprises granules, these granules 15 may be produced by techniques well known to those skilled in the art such as wet granulation, dry granulation (slugging), extrusion/spheronisation, fluid bed granulation and spray congealing. Further details on granulation processes may be found in the literature, for example Chapter 6, Pharmaceutical Principles of Solid Dosage Forms, J. T. Carstensen, Technomic, Lancaster, PA, 20 1993.

In addition to zolpidem or a pharmaceutically acceptable salt thereof, other ingredients may be incorporated into the granules. Such other ingredients include, but are not limited to diluents such as calcium phosphate, lactose, 25 dextrose, mannitol and microcrystalline cellulose, binders such as povidone (polyvinylpyrrolidone), methylcellulose, polyethylene glycol, gelatin and acacia, disintegrants such as starch, croscarmellose and crospovidone, glidants such as colloidal silica, and lubricants such as magnesium stearate and

hydrogenated vegetable oil. The granules may optionally contain chitosan, a salt or derivative or a salt of a derivative of chitosan.

Methods for preparation of microspheres are well known to those skilled in the art and include, but are not limited to, spray drying, interfacial polymerisation, coacervation/phase separation and solvent evaporation. Methods for producing microspheres are described in, for example, *Physicochemical Principles of Pharmacy*, 3<sup>rd</sup> Edition, pages 357 to 360, A T Florence and D Attwood, Macmillan, London, 1998 and *Physical Pharmacy*, 4<sup>th</sup> Edition, pages 516 to 519, A Martin, Wilkins and Wilkins, Baltimore, 1993. The microspheres may alternatively be produced using the methods described in WO98/30207 and the documents cited therein.

In addition to zolpidem or a pharmaceutically acceptable salt thereof, the microspheres used in the present invention may include ingredients that are known in the art to be suitable to be included in microspheres such as, but not limited to, starches, dextrans, gelatin, albumin, collagen, hyaluronic acid, chitosan, lactose, sucrose, dextrose, mannitol, methacrylate copolymers such as the Eudragit® polymers (Degussa, Germany), celluloses such as methylcellulose, and polyesters such as poly(lactide-co-glycolide).

The powder formulations of the present invention preferably have a zolpidem content of from 10 to 90% by weight (calculated as the free base), more preferably in the range 15 to 80% by weight and most preferably in the range 20 to 70% by weight.

If the powder formulations of the present invention comprise cyclodextrin, the ratio by weight of zolpidem or a pharmaceutical acceptable salt thereof

(calculated as the free base) to cyclodextrin is preferably from 1:0.25 to 1:10, more preferably from 1:0.5 to 1:8 and most preferably from 1:1 to 1:7.

If the powder formulations of the present invention comprise chitosan, a salt or derivative or a salt of a derivative thereof, they preferably have a chitosan content from 1 to 70% by weight, more preferably in the range 2 to 60% and most preferably in the range 5 to 50%.

The powder formulations of the invention preferably have a particle size in the range of from 10 to 900  $\mu\text{m}$ , more preferably from 10 to 600  $\mu\text{m}$  and most preferably from 10 to 300  $\mu\text{m}$ . More specifically, the mean particle size, expressed as the volume mean diameter ( $D_{50\%}$ ) and measured by a technique such as light microscopy combined with image analysis lies within these ranges. The  $D_{50\%}$  is preferably from 25 to 700  $\mu\text{m}$ , more preferably from 25 to 450  $\mu\text{m}$  and most preferably from 25 to 200  $\mu\text{m}$ . Furthermore, no more than 10% by volume of the particles have a diameter ( $D_{10\%}$ ) less than 10  $\mu\text{m}$  and at least 90% by volume of the particles have a diameter ( $D_{90\%}$ ) that does not exceed the upper limit of the size range.

It is desirable that the formulations of the invention do not contain substantial numbers of particles having a size below 10  $\mu\text{m}$  in order to minimise the possibility of delivery into the lungs.

The compositions of the invention may be administered to the nasal cavity in any suitable form. For example, the solutions of the invention may be administered to the nasal cavity in the form of drops or a spray and the powders of the invention may be administered in aerosolised form.

A preferred method of administering the solutions of the invention is using a spray device. Spray devices can be single ("unit") dose or multiple dose systems, for example comprising a bottle, pump and actuator, and are available from various commercial sources, including Pfeiffer (Germany), Valois 5 (France), Calmar (Germany), Ursatech (Germany), Bespak (UK) and Becton- Dickinson (USA). Electrostatic spray devices, such as described in US 5,655,517, are also suitable for the intranasal administration of the solutions of the invention.

10 For a spray device, the typical volume of liquid that is dispensed in a single spray actuation is from 0.01 to 0.14 ml, for example from 0.05 to 0.14 ml, such as 0.1 ml. It is a practical proposition to administer up to about 0.2 ml into each nostril (i.e. two x 0.1 ml sprays) to provide a therapeutic dose of drug, although the most acceptable dosing regimen would be one spray into one or 15 both nostrils. On the basis of administering a zolpidem tartrate dose of 10 mg as a total of one or two 0.1 ml sprays to each nostril, the drug concentration is preferably from 50 to 100 mg/ml zolpidem tartrate. Obviously, smaller spray volumes (or larger drug doses) could be administered if there was a corresponding increase in drug concentration i.e. a 10 mg dose could be 20 administered as a single 0.14 ml spray of a 71 mg/ml zolpidem tartrate solution or 0.28 ml of a 36 mg/ml zolpidem tartrate solution.

The powder formulations of the present invention are preferably administered to the patient in aerosolised form whereby energy from patient inhalation 25 (sniffing) is used to aerosolise the powder into the nasal cavity or where the device itself provides the aerosolisation energy, such as via compressed air. An example of the former device is manufactured by Pfeiffer and an example of the latter is the "Monopowder" manufactured by Valois.

The present invention also provides a nasal drug delivery device or a dose cartridge for use in a nasal delivery device loaded with a composition as defined above.

- 5 The present invention also provides processes for preparing the compositions of the invention. The process for preparing the solutions of the invention comprises mixing the components in a suitable solvent such as water. The powder compositions may be prepared using methods known in the art.
- 10 The compositions of the present invention have sleep-inducing properties and may be used in the treatment and/or prevention of insomnia. Thus, the present invention provides a method of administering zolpidem to a patient in need thereof, for example for the prevention or treatment of insomnia, which comprises the intranasal administration of a composition as defined above to
- 15 the patient.

The present invention also provides the use of zolpidem or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for nasal administration to a patient in need thereof. Such a medicament may have

- 20 sleep-inducing properties and may be used in the treatment and/or prevention of insomnia.

In the Figures:

- 25 Figure 1 shows the solubility of zolpidem tartrate in solutions containing SBE-CD and SBE-CB with chitosan.

Figure 2 shows plasma concentration curves following administration of intravenous and intranasal zolpidem formulations to sheep.

The invention is illustrated by the following non-limiting examples.

**Example 1 - Solubility of zolpidem tartrate in different cyclodextrins**

5

A semi-quantitative comparison was made of the ability of different cyclodextrins to enhance the aqueous solubility of zolpidem tartrate.

Aqueous solutions were prepared containing 200, 300 and 400 mg/ml of three types of cyclodextrin. These were hydroxypropyl- $\beta$ -cyclodextrin (HP-CD) (Cavamax® W7 HP Pharma, Wacker, Germany), methylated- $\beta$ -cyclodextrin (M-CD) (Cavamax® W7 M Pharma, Wacker) and sulfobutylether- $\beta$ -cyclodextrin (SBE-CD) (Captisol®, CyDex, USA). 25 mg samples of zolpidem tartrate (Zhejiang, Hangzhou, China) were added to a 0.5 ml portion of each cyclodextrin solution. The mixtures (containing 50 mg/ml drug) were stirred overnight at room temperature. If drug dissolved then more was added. If undissolved drug remained then an additional 0.5 ml of cyclodextrin solution was added and stirring continued. From this experiment an estimate could be made of zolpidem tartrate solubility in the different cyclodextrin solutions.

20

Results are summarised in Table 1.

*Table 1. Comparison of zolpidem solubility in different cyclodextrins*

CD concentration	Zolpidem tartrate solubility in CD (mg/ml)		
	HP-CD	M-CD	SBE-CD
200	25-31	25-31	>50
300	31-36	31-36	50-56
400	36-50	31-36	~60

All cyclodextrins tested enhanced the aqueous solubility of zolpidem tartrate. Of the cyclodextrins tested, SBE-CD was the most effective at enhancing the aqueous solubility of zolpidem tartrate.

5 **Example 2. - Solubility of zolpidem tartrate in SBE-CD**

The experiment described in Example 1 indicated that zolpidem tartrate solubility was highest in SBE-CD. Based on this result a more accurate determination of solubility in SBE-CD was performed, as follows:

10

A stock solution was prepared containing 400 mg/ml SBE-CD in water and then dilutions made to 100, 150, 200, 250 and 300 mg/ml. Into 2 ml portions of the stock and diluted SBE-CD solutions was dissolved 10 mg of chitosan glutamate (Protasan UPG213, NovaMatrix, Drammen, Norway). To each of 15 these samples of SBE-CD/chitosan solution and to each of six chitosan-free 2 ml samples of SBE-CD solutions were added 140 mg samples of zolpidem tartrate. The samples were left to stir overnight at room temperature (18°C). If during this time all the drug dissolved, further amounts were added until a suspension was formed (i.e. saturated drug solution formed). After further 20 stirring for up to 72 hours, suspensions were filtered (0.45 µm filter, Gelman, Portsmouth, UK) to recover saturated zolpidem tartrate solutions. The filtrate samples were diluted in water and the UV absorbance at 296 nm measured. By reference to a calibration curve of UV absorbance (296 nm) vs. zolpidem concentration, the concentration of zolpidem in the samples was calculated.

25 Solubility data are presented in Table 2 and presented graphically in Figure 1.

Table 2. Zolpidem solubility in SBE-CD solutions with and without chitosan

SBE-CD conc (mg/ml)	Zolpidem tartrate solubility (mg/ml)	Zolpidem tartrate solubility in presence of 5 mg/ml chitosan glutamate (mg/ml)
100	41.9	46.2
150	46.5	51.9
200	57.3	55.6
250	56.1	55.9
300	57.5	63.7
400	69.0	68.1

5 The data indicate that the enhancement of zolpidem tartrate solubility by SBE-CD appears to be relatively linear over the SBE-CD concentration range of 100-400 mg/ml. Chitosan appeared not to affect zolpidem solubility.

**Example 3 - Intranasal solution containing 50 mg/ml zolpidem tartrate and 200 mg/ml SBE-CD**

10 300 mg of 50% benzalkonium chloride solution (Albright & Wilson, Whitehaven, UK) was weighed into a 10 ml volumetric flask and 8 ml of water for injection added. The flask contents were stirred to disperse the benzalkonium chloride and then made up to volume with water. This produced 15 a stock solution containing 15 mg/ml benzalkonium chloride.

5 g of SBE-CD was weighed into a 25 ml volumetric flask and dissolved by adding approximately 15 ml of water followed by stirring. 1.25 g of zolpidem tartrate was added to the volumetric flask together with an additional 5 ml of

water and 0.25 ml of 15 mg/ml benzalkonium chloride stock solution. The solution was adjusted to approximately pH 4.5 by the addition of 0.1M hydrochloric acid solution (prepared by dilution of concentrated hydrochloric acid (Fisher)) and then made up to 25 ml with water. The solution was passed 5 through a 0.45  $\mu$ m membrane filter (Sartorius, Leicester, UK) and the pH measured. The final solution was at pH 4.6.

**Example 4 - Intranasal solution containing 50 mg/ml zolpidem tartrate, 200 mg/ml SBE-CD and 5 mg/ml chitosan glutamate**

10

10 g of SBE-CD and 250 mg of chitosan glutamate (Protasan UPG213, NovaMatrix, Drammen, Norway) were weighed and transferred into a 50 ml volumetric flask and dissolved by adding approximately 30 ml of water followed by stirring. 2.5 g of zolpidem tartrate was added to the volumetric 15 flask together with an additional 10 ml of water and 0.5 ml of 15 mg/ml benzalkonium chloride stock solution. The solution was adjusted to approximately pH 4.5 by the addition of 0.1M hydrochloric acid solution and then made up to 50 ml with water. The solution was passed through a 0.45  $\mu$ m membrane filter (Sartorius, Leicester, UK) and the pH measured. The final 20 solution was at pH 4.7.

**Example 5 - Solution for intravenous injection containing 1 mg/ml zolpidem tartrate**

25 50 mg of zolpidem tartrate was weighed into a 50 ml volumetric flask and dissolved by adding 40 mg of water. 445 mg of sodium chloride (Sigma, Poole, UK) was added to the volumetric flask and dissolved by stirring. The solution was made up to 50 ml by adding water. In a laminar flow cabinet the

solution was sterile filtered (0.2  $\mu\text{m}$  membrane filter) into sterile injection vials which were sealed with elastomeric closures and aluminium caps.

5 **Example 6 - Pharmacokinetic performance of intranasal zolpidem formulations in sheep**

The pharmacokinetic performance of the intranasal and intravenous zolpidem solutions described in Examples 3 to 5 was evaluated in sheep.

10 A group of five female sheep was used, each weighing around 45 kg. The formulations were administered to a randomised cross-over design. Each intranasal formulation (Examples 3 and 4) was administered at a zolpidem dose of 20 mg. This dose was provided by transferring 3.5 ml of the test formulation into a glass bottle, attaching a Valois VP7 spray pump and actuator to the bottle, priming the pump and then administering two 0.1 ml sprays into each nostril. For the intravenous dose, 5 mg of zolpidem was administered as a 15 5 ml bolus of the injection prepared in Example 5.

20 Blood samples were collected over a 360 minute period following dosing and plasma separated. Plasma samples were assayed by an HPLC method for zolpidem content. Pharmacokinetic parameters were calculated from the plasma data.

25 A summary of pharmacokinetic parameters is provided in Table 3. Plasma concentration versus time curves are provided in Figure 2.

The pharmacokinetic data indicate rapid absorption of zolpidem following intranasal administration ( $T_{\max}$  values of 13 and 16 minutes). In addition, the

bioavailability was significantly enhanced by the inclusion of chitosan in the intranasal solution formulation.

5 *Table 3. Summary of pharmacokinetic parameters following administration of zolpidem intranasal and IV injection doses to sheep (mean, n=5 [SD]).*

Dose group	T <sub>max</sub> (min)	C <sub>max</sub> (ng/ml)	AUC (ng/ml.min)	Absolute bioavailability (%)
Nasal solution (Example 3)	13 [8]	18 [3]	1328 [544]	10 [4]
Nasal solution + 5 mg/ml chitosan (Example 4)	16 [5]	40 [11]	2822 [786]	22 [6]
IV injection (Example 5)	0 [0]	109 [28]	3298 [684]	100

**Example 7 - Preparation of zolpidem tartrate/chitosan glutamate powder blend**

10 5 g of zolpidem tartrate, 3 g of chitosan and 2 g of lactose (InhaLac® 120, Meggle, Germany) are weighed into a glass bottle. The lid is attached to the bottle, which is placed into a Turbula T2C mixer (Willy Bachofen, Bubendorf, Switzerland). The bottle contents are mixed at speed setting 2 for 30 minutes. A 10 mg sample of the powder blend is filled into a Monopowder nasal spray

15 device (Valois, Marly-le-Roi, France). When actuated, this device will deliver 10 mg of powder, equivalent to 5 mg of zolpidem tartrate.

**Example 8 - Preparation of zolpidem tartrate/SBE-CD/chitosan glutamate powder blend**

12 g of SBE-CD is weighed into a 100 ml flask and dissolved in 30 ml of  
5 water. 6 g of zolpidem tartrate is added to the SBE-CD solution and stirred for  
60 minutes. The resulting suspension is frozen in liquid nitrogen and freeze-  
dried for 72 hours. The freeze-dried product is passed through a 0.25 mm mesh  
size sieve and 15 g transferred to a glass bottle. 2.5 g of chitosan glutamate and  
2.5 g of lactose (InhaLac® 120) are added to the bottle, which is sealed and  
10 placed into a Turbula T2C mixer. The bottle contents are mixed at speed  
setting 2 for 30 minutes. A 20 mg sample of the powder blend is filled into a  
Monopowder nasal spray. When actuated, this device will deliver 20 mg of  
powder, equivalent to 5 mg of zolpidem tartrate.

## CLAIMS:

1. A composition for nasal delivery comprising zolpidem or a pharmaceutically acceptable salt thereof.

5

2. A composition according to claim 1 in the form of a solution or a powder.

10

3. A composition according to claim 2 in the form of an aqueous solution.

4. A composition according to any one of the preceding claims comprising a salt of zolpidem selected from the hydrochloride, mesilate, citrate, nitrate, lactate, maleate, tartrate, phosphate, succinate, fumarate and gluconate salts.

15

5. A composition according to claim 4, wherein the salt is the tartrate salt.

20

6. A composition according to any one of the preceding claims, which is in the form of a solution and comprising from 16 to 97 mg/ml of zolpidem (expressed as the free base).

7. A composition according to claim 6, comprising from 24 to 80 mg/ml of zolpidem (expressed as the free base).

25

8. A composition according to any one of the preceding claims in the form of a solution and comprising a solubility enhancing agent.

9. A composition according to claim 8, wherein the solubility enhancing agent is a cyclodextrin.

10. A composition according to claim 9, wherein the cyclodextrin is sulfobutylether- $\beta$ -cyclodextrin (SBE-CD).
- 5 11. A composition according to claim 10, comprising 50 to 700 mg/ml SBE-CD.
12. A composition according to any one of the preceding claims having a pH of from 4.0 to 7.0.
- 10 13. A composition according to any one of the preceding claims additionally comprising chitosan, a salt, a derivative thereof or a salt of a derivative thereof.
- 15 14. A composition according to claim 13, comprising from 0.5 to 50 mg/ml of chitosan, a salt, a derivative thereof or a salt of a derivative thereof.
- 15 15. A composition according to claim 13, which is an aqueous solution and comprises from 30 to 60 mg/ml of zolpidem tartrate, 100 to 300 mg/ml SBE-CD and 2 to 10 mg/ml of chitosan glutamate.
- 20 16. A composition according to any one of claims 1, 2 and 4 to 14, in the form of a non-aqueous solution.
- 25 17. A composition according to claim 16, comprising at least one of ethanol, propylene glycol, polyethylene glycol, glycofurool, benzyl benzoate and a polyoxyethylene castor oil derivative.

18. A composition according to any one of claims 1, 2, 4 and 5 in the form of a powder.
19. A composition according to claim 18, wherein the powder contains granules or microspheres.
20. A composition according to claim 18 or 19, comprising 20 to 70 % by weight of zolpidem (expressed as free base).
21. A composition according to any one of claims 18 to 20, further comprising a means for improving the rate of dissolution of zolpidem in the nasal cavity.
22. A composition according to claim 21, wherein the means is a cyclodextrin.
23. A composition according to claim 22, wherein the ratio by weight of zolpidem or a pharmaceutically acceptable thereof to cyclodextrin is from 1:0.25 to 1:10.
24. A composition according to claim 22 or 23, wherein the cyclodextrin is sulfobutylether- $\beta$ -cyclodextrin (SBE-CD).
25. A composition according to any one of claims 18 to 24, further comprising chitosan, a salt, a derivative thereof or a salt of a derivative thereof.

26. A composition according to claim 25, comprising from 5 to 50 % by weight of chitosan, a salt, a derivative thereof or a salt of a derivative thereof.

5 27. The use of zolpidem or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for nasal administration to a patient in need thereof.

10 28. Use according to claim 27 in the manufacture of a medicament for the treatment or prevention of insomnia.

15 29. A method of administering zolpidem or a pharmaceutically acceptable salt thereof to a patient in need thereof, which method comprise the intranasal administration of a composition as defined in any one of claims 1 to 26.

30. A method of treating or preventing insomnia, which method comprises the intranasal administration of a composition as defined in any one of claims 1 to 26.

20 31. A nasal drug delivery device or a dose cartridge for use in a nasal drug delivery device comprising a composition as defined in any one of claims 1 to 26.

**ABSTRACT****INTRANASAL COMPOSITIONS**

5 The present invention provides compositions for the intranasal administration of zolpidem or a pharmaceutically acceptable salt thereof. Preferred compositions of the invention are in the form of aqueous solutions. Optionally the compositions of the invention comprise a cyclodextrin and/or chitosan, a salt or derivative thereof or a salt of a derivative of chitosan. The compositions  
10 can be used for the treatment or prevention insomnia.

1. *zolpidem*  
2. *zolpidem*  
3. *zolpidem*

Figure 2. Plasma concentration curves following administration of intravenous and intranasal zolpidem formulations to sheep (mean of five animals)

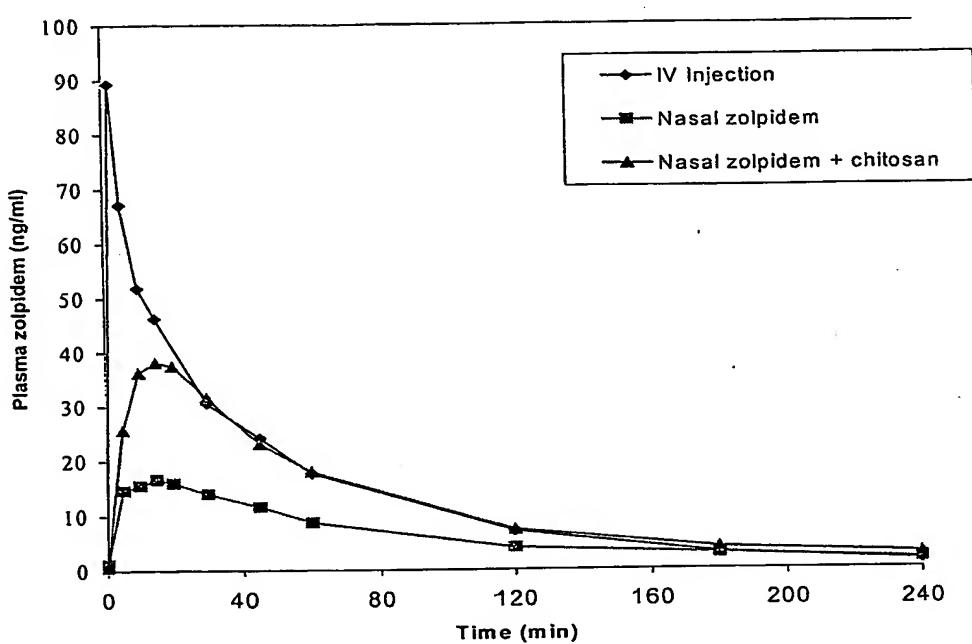
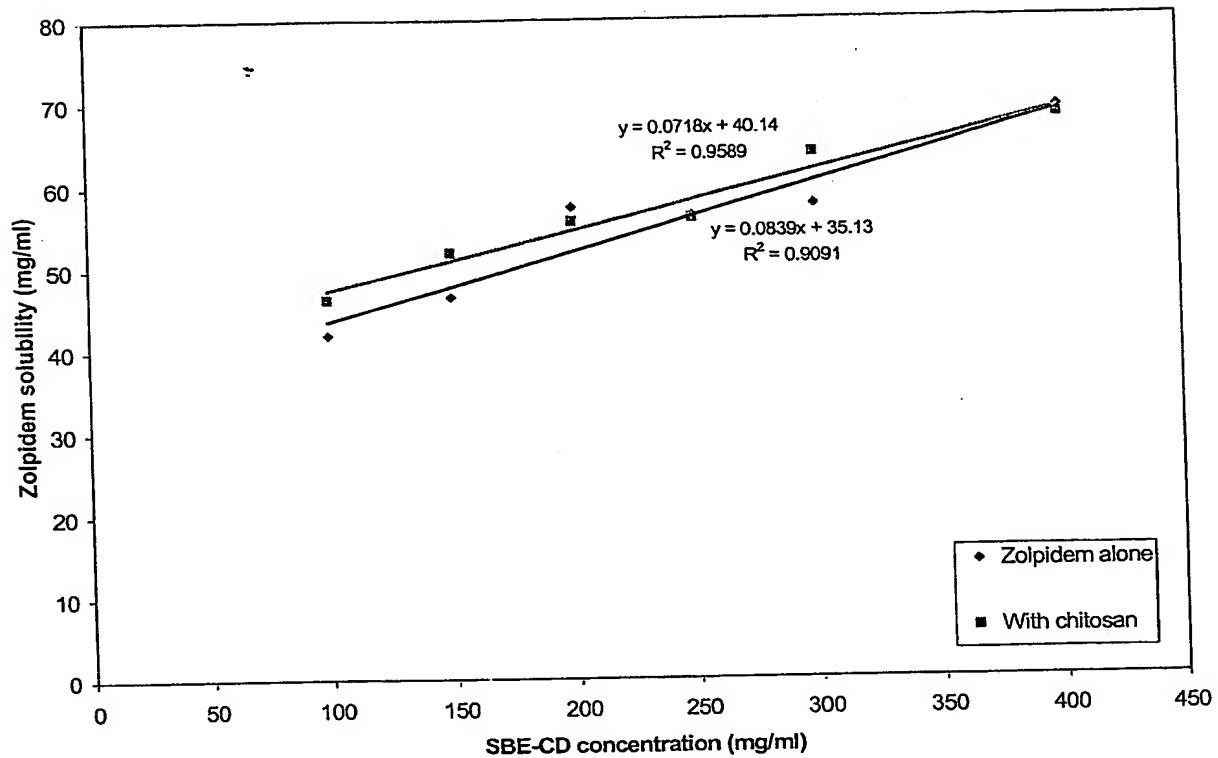


Figure 1. Solubility of zolpidem tartrate in solutions containing SBE-CD and SBE-CD + chitosan (lines of best fit shown)



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